Overview of Activities in the European Union - Present and Future Tasks

New Trends and the Role in International Co-operation

European Medicines Agency
Dr. John Purves
Content

- Introduction: Environmental & legislative changes
- New legislation: new tools for medicinal product review
- Novel products and new developments
- Looking ahead
Introduction

- European Medicines Agency (EMEA) – decentralised body of EU

- The mission of the EMEA is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health.

- Responsible for centralised procedure and co-ordination of EU network + plays a role in stimulating innovation and research in the pharmaceutical sector.
Introduction

- **Preparing for the future:**
  - Environmental and legislative changes, as well as evolution in science pose both challenges and opportunities to the Regulatory Authorities

- **Environmental changes**
  - Institutional changes, such as EU enlargement
  - Economic and social changes: globalisation, active participation EU citizens, transparency and communication requirements
  - Scientific changes: new technologies, availability of medicines, unmet medical needs
Introduction

- **International dimension of EMEA activities**
  - International Conference on Harmonisation (ICH): Guidelines applicable for EU, USA, Japan
  - ICH and EMEA Guidelines also used outside ICH region
  - Confidentiality agreements with USA, Japan, Canada, Switzerland, Australia, New Zealand (India), (Russia), (China)
  - Interactions with WHO, e.g. on vaccines (pandemic) and Biosimilars
  - Bilateral interactions with FDA (‘Clusters’) on specific topics, such as PhVig, Oncology, Pandemic vaccines, ATMP
Introduction

- **Legislative changes**
  - Revision of pharmaceutical legislation (2004)
  - Paediatric legislation (2006)
  - Regulation on Advanced therapies (2007)

- **Evolution in science**
  - Novel products coming in for scientific advice or marketing authorisation
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Centralised procedure

- 1 Assessment
- Scientific Committee: CHMP
  Committee for Medicinal Products for Human Use
- Maximum time limit
  210 days evaluation to CHMP Opinion → Decision (MA)
- 1 Marketing Authorisation valid whole EU
- 1 Invented name
- 1 Common Labelling (all EU languages identical)
  Summary of Product Characteristics
  User Package Leaflet & Package Labelling
New regulatory tools – Conditional marketing authorisation

- Authorisation **valid for 1 year**, renewable
- Allows for **increased flexibility** when granting a MA
- **Conditions**: unmet medical need and benefit to public health of immediate availability overweighs risks inherent that additional data is required.
- Limited to medicinal products:
  - Aimed at preventing, treating or for medical diagnosis of seriously debilitating or life-threatening diseases,
  - **Emergency threats** (WHO, EC)
  - **Orphan** medicinal products
New regulatory tools – Accelerated review

• **Accelerated review**
  » **150 days** instead of 210 days
    – Possibility to revert back to normal timetable during the procedure
  » For products with **major public health interest** – therapeutic innovation
New regulatory tools – Risk management plans

- **Risk management system** is a set of pharmacovigilance activities and interventions designed to **identify, characterise, prevent or minimise risks** relating to medicinal products, including **risk communication** and assessment of **risk minimisation** interventions.

- **Risk Management Plan**: to be submitted with all new MAA (legal requirement). RMP describes / addresses:
  1. Safety Specification
  2. Pharmacovigilance Plan (Routine – Additional PhVig activities)
  3. Evaluation of the need for risk minimisation measures
  4. Risk Minimisation Plan (if needed)
New regulatory tools – Paediatric Investigation Plan (PIP)

- System of both obligations and Rewards for all med. prod.:
  - Med. products under development and yet to be authorised
    • Have to submit results of PIP (agreed by PDCO) at time of marketing authorisation application (unless waiver or deferral)
    • 6-month extension of the Supplementary Protection Certificate
  - Med. products still covered by intellectual property (IP) rights
    • Have to submit results of agreed PIP at time of change (variation/extension) for new indication, route of administration, or pharmaceutical form
    • 6-month extension of the Supplementary Protection Certificate
  - Authorised medicinal products no longer covered by IP rights
    • new Paediatric Use Marketing Authorisation covering exclusively paediatric indication(s) and formulation(s)
    • 10 years data protection
New regulatory tools – Small and Medium Enterprises (SMEs)

- SME provisions
  » Reduced / deferred fees
  » Administrative assistance & assistance for translations
  » Scientific advice
Suggestions

- Authorities and industry should communicate at a very early time-point to:
  » Create greater awareness with Authorities on products in the pipeline
  » Discuss and anticipate hurdles:
    – Scientific issues
    – Regulatory problems
  » Allow authorities to:
    – Gain insight in hurdles to product development
    – Prioritise their activities (e.g. guideline development)
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Biosimilars
(abridged biologicals)

- Legislation states:

  » Where there are differences (particularly) in raw materials or manufacturing processes of biosimilar and reference product, then results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.

  » The results of other tests and trials from the reference medicinal product’s dossier shall not be provided

  » Article 10(4) of Directive 2001/83/EC, as amended (abridged but not generic)
# Dossier requirements for biosimilars

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- **Cross reference – class specific Safety and Efficacy**
- **Integrated Comparability Exercise – product specific Quality, Safety and Efficacy**
Current Biosimilar Guidelines – Summary

Overarching Guideline (CHMP/437/04).
“Guideline on Similar Biological Medicinal Products”

Biotechnology- derived proteins

Quality

Non-clinical

Clinical

General guidelines

Defines philosophy and principles

Annex guidelines - specific data requirements

Insulin Somatropin GCSF Epoetin (under revision) IFN-α LMMH

Non-clinical Non-clinical Non-clinical Non-clinical Non-clinical Non-clinical

Clinical Clinical Clinical Clinical Clinical Clinical
<table>
<thead>
<tr>
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<th>Status</th>
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<td>1</td>
<td>Omnitrope (somatropin)</td>
<td>Sandoz</td>
<td>Authorised</td>
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<tr>
<td>2</td>
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<td>Biopartners</td>
<td>Authorised</td>
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<td>3</td>
<td>Alpheon (interferon alfa)</td>
<td>Biopartners</td>
<td>Negative</td>
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<tr>
<td>4</td>
<td>Binocrit (epoetin alfa)</td>
<td>Sandoz</td>
<td>Authorised</td>
</tr>
<tr>
<td>5</td>
<td>Epoetin alfa Hexal (epoetin alfa)</td>
<td>Hexal</td>
<td>Authorised</td>
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<tr>
<td>6</td>
<td>Abseamed (epoetin alfa)</td>
<td>Medice</td>
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<tr>
<td>7</td>
<td>Silapo (epoetin zeta)</td>
<td>Stada</td>
<td>Authorised</td>
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<tr>
<td>8</td>
<td>Retacrit (epoetin zeta)</td>
<td>Hospira</td>
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Biosimilars
International Cooperation

- **EMEA contributing to guidance of international partners**
  - Health Canada
  - Japan
  - WHO
  - FDA (liaison pending legislation)

- **EMEA guidance also adopted by, e.g.:**
  - Australia
  - Malaysia
Regulation on Advanced Therapies
Key elements

- **Advanced Therapy medicinal products (ATMP)**
  - Gene therapy products
  - Somatic Cell therapy products
  - Tissue engineered products

- **Principles of existing legislation on medicines apply to advanced therapies**

- **New legislation provides incentives for companies developing ATMP**
  - Fee reductions, certification procedure (SME)
Advanced Therapies

Legislation

Medical Devices 93/42/EEC
Regulation on Advanced Therapies
Medicinal Products 2001/83/EC

Science

Advanced Therapies

Medical Devices
Tissue Engineering
Cell Therapy
Gene Therapy
Biotech (e.g. insulin)
Pharmaceuticals (e.g. aspirin)

NEW Committee for Advanced Therapies (CAT)
Specific expertise

CHMP expertise
Evaluation procedure for ATMP

- Centralised procedure mandatory:
  - pooling of Community expertise
  - harmonised requirements & evaluation
  - ensure uniform and direct access to market

- New Committee for Advanced Therapy products (CAT)
  - Specific expertise required (e.g. surgery, medical devices)
  - Will prepare a draft opinion for final CHMP approval

- Scientific & procedural guidelines under development
New developments in the vaccine area

- Novel vaccines
  - Human Papiloma virus vaccines
  - Pandemic and Prepandemic vaccines
  - Others under development (eg Malaria vaccines)

- ‘Article 58’ procedure: scientific evaluation on behalf of WHO
Pandemic Influenza

1. Guidelines on pandemic influenza vaccines & establishment of a fast-track procedure:

2. Guideline on influenza vaccine prepared from strains with a pandemic potential and for use outside of the core dossier context
Pandemic vs Pre-pandemic influenza vaccine

- **Pandemic influenza vaccines** ideal vaccines (full protection against pandemic virus), but:
  - Stockpiling not possible (strain unknown)
  - At least 3 months before vaccine becomes available
  - Limited supply, most vaccine only after 1st wave
  - Need for a special regulatory framework to allow fast-track approval: core dossier approach.

- **Pre-pandemic vaccines** can be stockpiled but:
  - Estimated guess of what strain will cause the pandemic (e.g. H5N1)
  - Level of protection unknown: stockpiled vaccine might not be useful
  - Standard approval procedure apply.
Fast-track approval of pandemic influenza vaccines

- Approval of mock-up vaccines *(core dossiers)* in the interpandemic period
- Fast-track approval of the pandemic vaccine after announcement of pandemic *(variation to core dossier)*
- Core dossier approach limits risk that non-effective/non-safe pandemic vaccines will be used during pandemic
- **3 Mock-up vaccines already approved** → 3-days approval process of Pandemic vaccine
  - Daronrix (GSK Bio)
  - Focetria (Novartis)
  - Pandemrix (GSK Bio)
Approval of Pre-pandemic vaccines

- A regulatory framework and specific guidance is in place in the EU for the authorisation of ‘pre-pandemic’ influenza vaccines

- Potential uses: stockpiling, use from WHO phase 3 onwards, prime-boost strategies, use in early stages of pandemic
  - No recommendation of specific use in EMEA guideline: responsibility of Public Health Authorities in EU Member States

- 1 Pre-pandemic influenza vaccines approved: Prepandrix
‘Article 58’ Procedure

Facilitating the licensure of vaccines predominantly for the developing world

Article 58 of Regulation (EC) No. 726/2004

‘CHMP Scientific Opinion in cooperation with WHO’
ICH 8 – 11 Guidelines

ICH Q8 & Q8R

» “Quality by Design” in Pharmaceutical Development
» Principles and application (product)
» Concept of Design Space
» PAT can facilitate process knowledge

ICH Q11

» Drafting ongoing
» Aim to apply QbD principles to active substances (chemical / biological), without neglecting traditional approaches to manufacture.
Variations Regulation

- **Regulation in force – December 2008**
  - Aim for flexibility
  - Allows for Design Space approach
  - Guideline to provide detailed scopes
    - (drafting ongoing)

- **Types of variation:**
  - IA, IB, II (Similar to CBE, CBE-30, PAS)
  - Also annual reporting for some changes
  - Changes to biological actives: Type II
Guideline on
“Development, production, characterization and specifications for monoclonal antibodies and related products”

- Replaces the “old” guideline (3AB4a, December 1994).
- Scope: - Quality issues for marketing authorisation of MAbs for therapeutic, prophylactic and in vivo diagnostic use.
  - Applicability to MAb-related products (e.g. fragments, conjugates, fusion proteins, bispecific antibodies) on a case-by-case basis.
  - MAbs used in clinical trials not addressed.
- Extensive consultation with Industry:
  - Written comments during public consultation (June-November 2007);
  - Expert meeting organised at EMEA in June 2008: discussion e.g. on platform manufacturing and flexibility of requirements including viral safety aspects; setting of specifications including glycosylation.
  → Number of comments from Industry implemented in the guideline
- Next steps:
  - Specific annexes to the guideline on MAb-related products may be developed in the future.
  - Workshop to be organised at EMEA (June/July 2009) on quality, non clinical and clinical aspects for biosimilar MAbs.
Guideline on
“Allergen products: production and quality issues”

- Scope: allergen products of biological origin: manufacture, characterization, quality control including the establishment and use of in-house reference preparations and sera pools.
- Guidance is provided on recombinant allergen products (not addressed in the “old” guideline).
- A new concept of homologous groups is described, with guidance on grouping of allergen extracts and extrapolation of data within a group.
- This quality guideline was revised in parallel with:
  - The revision of the Ph. Eur. monograph on “Allergen products” (adopted by the Ph. Eur. Commission in November 2008, will come into effect in January 2010);
  - The development of the guideline on “Clinical development of products for specific immunotherapy for the treatment of allergic diseases” (published in December 2008).

→ consistency and complementarity between these 3 documents
Guideline on products from Transgenic animals/plants

- **Products from Transgenic animals**
  - Guideline on the use of transgenic animals in the manufacture of biological medicinal products for human use (1995) – start of revision planned in 2009
  - 2 products submitted for MA:
    - **ATryn** (Antithrombine alfa, from transgenic goat) – Authorised in July 2006
    - **Rhucin** (recombinant C1 inhibitor, from transgenic rabbits) – Negative opinion March 2008

- **Products from Transgenic plants**
  - Guideline of the quality of biological actives substances produced by stable transgene expression in higher plants (published July 2008)
  - No products yet submitted for MA.
Guidelines on biological Investigational Medicinal Products (IMPs)

Important progress to provide an harmonised approach in EU for industry and regulators for assessment of quality of IMPs during clinical development (especially beneficial for multi-centre studies):
Guidelines on biological Investigational Medicinal Products (IMPs)

- Guideline on virus safety evaluation of biotechnological investigational medicinal products (adopted Jul 2008 – applicable as of Feb 2009)
  » outlines the viral safety requirements applicable to all stages of clinical development of an IMP
  » covers monoclonal antibodies and recombinant DNA derived IMPs including recombinant subunit vaccines (but not other vaccines)
  > Extensive consultation with and comments from industry during drafting: high interest for guideline!
Guidelines on biological Investigational Medicinal Products (IMPs)

- Guideline on the chemical and pharmaceutical quality documentation concerning biological Investigational Medicinal Products in Clinical Trials (first draft under development, planned for release during second half of 2009)
  - will address specific aspects relevant to products under development and should help to identify the essential quality requirements
  - Covers biological/biotechnology products (i.e. recombinant proteins)
  - Extensive comments from industry also expected for this guideline
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Looking ahead (1/4)

- Both authorities and innovators have a role to play:
  - At what stage can the authorities (e.g. EMEA) facilitate the development and marketing authorisation of innovative medicines?
  - What can the innovators (Academia / SME & Innovative Pharma) do to speed up the market access of innovative medicines?
Looking ahead – Authorities’ role (2/4)

- **Scientific Innovation: a moving target**
  - Keeping up to date with scientific progress and its potential benefit for public health
  - Knowledge management: how to handle the corpus of scientific knowledge and how to find keep the experts needed for scientific review
  - Flexibility needed to integrate different disciplines and regulatory frameworks
  - Use of new review tools
  - Global market and EMEA / FDA Interactions
Looking ahead – Authorities’ role (3/4)

- Regulatory challenges: rules cannot stand still
  - Regulatory requirements must **reflect** scientific progress, not **define** scientific pathways
  - Authorities should not become complacent about using established methodologies
  - New ways of ensuring compliance in a changing environment (pre- and post-licensing)
  - Greater regulatory transparency, with more complex risk communication issues
  - International cooperation to establish common rules that take into account different interests
Academic (basic) research is urgently needed on new tools for demonstrating safety and efficacy of innovative medicines, for example:

» New animal or computer-based predictive models
» New biomarkers and surrogate markers for safety and efficacy
» Alternative methodologies or combination of methodologies to monitor and predict quality, safety, efficacy and risk management systems
» New clinical evaluation techniques
» Improvement of existing methodologies, e.g. characterisation of biotech molecules
Regulators’ responsibilities

“We support research and innovation to stimulate the development of better medicines”

(new EMEA mission statement)

- Provide for transparent, predictable, science-based regulatory processes
- Ensure timely uptake of innovation into regulatory requirements
- Engage in transparent dialogue with stakeholders (industry, academia, etc.)
- Co-ordinate the input from the EU network into relevant activities at global level
Important Parameters for the EMEA

Idea stimulated by the book entitled “Consilience” – the unity of knowledge, by Edward O. Wilson

Thank you for your attention

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For further reading

EMEA Website: http://www.emea.europa.eu

Advanced Therapies
http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm

Pandemic influenza

Biosimilars